Electrophysiological properties of intravenous metoprolol in man

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SUMMARY Electrophysiological changes produced by intravenous (0·1 mg/kg) metoprolol, a new selective β_1-blocking agent devoid of intrinsic activity, were studied in 16 subjects with estimated normal impulse formation and conduction.

The most important effects were sinus bradycardia, mild increase of sinoatrial conduction time, depression of intranodal conduction, and prolongation of AV node refractory periods. Sinus node recovery time and atrial refractory periods were unmodified. Infranodal conduction and the refractory periods of the His-Purkinje system, as well as of the bundle-branches, were unchanged.

These effects are compared with those observed after intravenous propranolol, pindolol, and oxprenolol.

During the past 10 years a number of adrenergic β-receptor antagonists, e.g. propranolol, alprenolol, pindolol, oxprenolol, and practolol, have been widely used in the treatment of angina, hypertension, and arrhythmias. Of these drugs, only practolol proved to be a selective inhibitor of β_1 receptors. Recently, another β_1-selective blocker, metoprolol[1], has been described. Unlike practolol, this compound is devoid of β-receptor stimulating properties, that is 'intrinsic activity' (Ablad *et al.*, 1973, 1975). Metoprolol is equipotent to propranolol as regards blockade of the cardiac response to sympathetic nerve stimulation, of cardiac lipolytic and renin release responses to noradrenaline (Ablad *et al.*, 1975), and is almost equipotent as regards inhibition of the tachycardic response to exercise (Johnsson, 1975). Metoprolol has been shown to be relatively devoid of propranolol's local anaesthetic effect which can produce cardiodepression (Ablad *et al.*, 1973). No studies have been made to test the electrophysiological properties of this drug.

The present work was undertaken to determine the electrophysiological effects of intravenously administered metoprolol in 16 human subjects with estimated normal impulse formation and conduction.

[1]Metoprolol is also known as H 93/26 (AB Hassle, Sweden) and CGP 2175 (Ciba-Geigy AG, Switzerland).

Subjects and methods

Studies were carried out on 16 subjects who underwent a His bundle electrogram study because of a history of cardiac arrhythmia. Informed consent was obtained from all subjects. Clinical data are presented in Table 1. All subjects were in sinus rhythm and had QRS duration of less than 0·12 s and normal conduction intervals as measured by His bundle recording technique (Scherlag *et al.*, 1969). Cardiac drugs were withheld for at least 72 hours before beginning the study.

Table 1 *Clinical data of 16 cases who entered study*

Patients	Age (y)	Sex	Cardiac diagnosis	Indication for electrophysiological study
1	58	M	ASHD	Atrial extrasystoles
2	69	M	ASHD	Atrial extrasystoles
3	47	F	NHD	Paroxysmal atrial fibrillation
4	63	M	ASHD	Ventricular extrasystoles
5	37	M	NHD	Atrial extrasystoles
6	41	M	ASHD	Ventricular extrasystoles
7	47	M	ASHD	Paroxysmal atrial fibrillation
8	58	M	ASHD	Ventricular extrasystoles
9	48	M	ASHD	Ventricular extrasystoles
10	33	M	NHD	Paroxysmal atrial fibrillation
11	48	M	ASHD	Ventricular extrasystoles
12	54	M	ASHD	Atrial extrasystoles
13	47	M	ASHD	Paroxysmal atrial flutter
14	45	M	ASHD	Paroxysmal atrial tachycardia
15	55	M	NHD	Paroxysmal atrial tachycardia
16	43	M	ASHD	Paroxysmal atrial fibrillation

ASHD, atherosclerotic heart disease; NHD, no heart disease.

Electrode catheters were introduced percutaneously into the right femoral vein. A 6F bipolar catheter was positioned across the tricuspid valve to record His bundle electrograms; a 6F quadripolar catheter was positioned against the lateral wall of the right atrium near its junction with the superior vena cava. Proximal electrodes were used to record high atrial electrograms and distal electrodes were connected to a DTU 110 external pulse generator[1] for pacing. Standard leads I, III, and V1 and intracardiac electrograms were displayed on a multichannel oscilloscope and recorded at 100 mm/s paper speed on an 8-channel Hewlett-Packard 4368 C photographic recorder at a frequency setting of 50 to 500 Hz. Basic unstimulated intervals were recorded first.

In 11 patients (group A), controlled drive stimuli S_1 were delivered to the high right atrium: S_1 was first adjusted to a rate just fast enough to ensure atrial capture. S_2 was then introduced in 10 to 20 ms decrements, after every eighth S_1, until no intracardiac response occurred. Stimuli pulses were rectangular, 2 ms in duration, and approximately twice the diastolic threshold. Fast atrial pacing was subsequently performed, increasing the heart rate by 10 beats per minute during each test, until a second degree type I supra-His AV block was produced. A_1, H_1, and V_1 were atrial His bundle, and ventricular electrograms induced by S_1; A_2, H_2, and V_2 were corresponding electrograms induced by S_2.

In 5 patients (group B), premature atrial stimuli were introduced after every eight sinus beats and moved in 20 ms increments, using the R wave to trigger the stimulator. In this way, the entire atrial diastolic period was scanned for determination of mean sinoatrial conduction time (SACT). To evaluate sinus node automaticity, atrial pacing at three different heart rates (120/min, 130/min, and 140/min) for periods of one minute, was performed. After each atrial pacing, a rest period of 30 s was given to allow the rhythm to return to its basic level.

All studies were performed before and 2, 15, and 30 minutes, respectively, after 0·1 mg/kg metoprolol had been administered intravenously for 2 minutes.

Definition of terms

Atrial effective refractory period was the longest S_1–S_2 interval at which atrial capture failed to occur. Atrial functional refractory period was the shortest A_1–A_2 attainable. AV nodal effective refractory period was the longest A_1–A_2 interval which did not propagate to the His bundle. AV nodal functional

[1]Manufactured by M. Bloom, Philadelphia, USA.

Table 2 *Effects of metoprolol on sinus cycle lengths, intra-atrial, intranodal, and intraventricular conduction in man*

Cases		Sinus cycle	PA	AH	HV	QRS
1	Control	760	40	90	40	90
	After 2 min	900	40	110	40	90
	After 15 min	910	40	110	40	90
	After 30 min	860	40	110	40	90
2	Control	710	30	90	45	110
	After 2 min	910	30	100	45	110
	After 15 min	880	30	100	45	110
	After 30 min	870	30	100	45	110
3	Control	720	30	80	35	90
	After 2 min	850	30	95	35	90
	After 15 min	830	30	95	35	90
	After 30 min	820	30	80	35	90
4	Control	1050	30	60	45	90
	After 2 min	1000	30	60	45	90
	After 15 min	960	30	60	45	90
	After 30 min	920	30	60	45	90
5	Control	940	25	70	40	100
	After 2 min	990	25	75	40	100
	After 15 min	950	25	75	40	100
	After 30 min	910	25	75	40	100
6	Control	910	30	120	50	110
	After 2 min	930	30	120	50	110
	After 15 min	960	30	120	50	110
	After 30 min	950	30	120	50	110
7	Control	900	30	90	40	100
	After 2 min	1100	30	100	40	100
	After 15 min	1090	30	100	40	100
	After 30 min	1110	30	100	40	100
8	Control	1090	25	110	40	70
	After 2 min	1220	25	110	40	70
	After 15 min	1210	25	110	40	70
	After 30 min	1150	25	110	40	70
9	Control	930	30	80	50	90
	After 2 min	970	30	80	50	90
	After 15 min	960	30	80	50	90
	After 30 min	910	30	80	50	90
10	Control	950	30	90	35	90
	After 2 min	1070	30	100	35	90
	After 15 min	1090	30	100	35	90
	After 30 min	1010	30	100	35	90
11	Control	870	35	80	45	90
	After 2 min	950	35	100	45	90
	After 15 min	960	35	100	45	90
	After 30 min	970	35	100	45	90
12	Control	920	30	110	40	110
	After 2 min	1080	30	110	40	110
	After 15 min	1010	30	130	40	110
	After 30 min	1010	30	130	40	110
13	Control	1030	20	90	40	90
	After 2 min	1120	20	100	40	90
	After 15 min	1180	20	100	40	90
	After 30 min	1030	20	100	40	90
14	Control	1100	35	80	35	80
	After 2 min	1080	35	90	35	80
	After 15 min	1070	35	90	35	80
	After 30 min	1200	35	90	35	80
15	Control	810	35	80	40	90
	After 2 min	880	35	90	40	90
	After 15 min	890	35	90	40	90
	After 30 min	850	35	90	40	90
16	Control	750	30	120	40	100
	After 2 min	870	30	120	40	100
	After 15 min	820	30	120	40	100
	After 30 min	810	30	120	40	100
*Control		902 ± 126	30 ± 4	90 ± 17	41 ± 4	93 ± 10
After 2 min		995 ± 106	30 ± 4	97 ± 16	41 ± 4	93 ± 10
After 15 min		985 ± 115	30 ± 4	98 ± 17	41 ± 4	93 ± 10
After 30 min		961 ± 116	30 ± 4	97 ± 18	41 ± 4	93 ± 10

*All values in ms.
Significance of difference from control: † < 0·01; ‡ < 0·02; § < 0·05

refractory period was the shortest propagated H_1–H_2 interval. Effective and functional refractory periods of the His-Purkinje system were, respectively, the longest H_1–H_2 interval not propagated to the ventricle and the longest H_1–H_2 interval followed by an increase in the H_2–V_2 interval. The relative refractory period of a bundle-branch was considered the longest H_1–H_2 interval producing the electrocardiographic pattern of complete bundle-branch block.

Wenckebach point was the lowest driven atrial rate producing AV nodal Wenckebach periods.

Mean sinoatrial conduction time (SACT) was calculated from the formula

$$SACT = \frac{A_2\text{–}A_3 - A_1\text{–}A_1}{2}$$

(Strauss *et al.*, 1973). Sinus node recovery time was the pause observed after overdrive pacing, and it was defined as the interval from the last paced P wave to the first spontaneously occurring P wave, and expressed as a percentage (pause/control P-P × 100) (Mandel *et al.*, 1971).

Results are presented as the mean ± standard error using Student's t test for paired data. Differences were considered significant when P was less than 0·05.

Table 3   *Effects of metoprolol on sinus node automaticity and sinoatrial conduction in man*

Cases	SNRT 120/min	130/min	140/min	SACT (ms)
12 Control	109%	117%	96%	92
After 2 min	115%	113%	117%	102
After 15 min	115%	127%	127%	106
After 30 min	115%	121%	129%	94
13 Control	118%	122%	122%	92
After 2 min	123%	122%	122%	135
After 15 min	112%	113%	102%	92
After 30 min	129%	114%	105%	92
14 Control	120%	132%	119%	131
After 2 min	133%	130%	115%	149
After 15 min	129%	107%	108%	120
After 30 min	131%	139%	116%	113
15 Control	118%	134%	122%	70
After 2 min	125%	143%	139%	79
After 15 min	133%	150%	137%	81
After 30 min	139%	133%	135%	58
16 Control	117%	124%	133%	92
After 2 min	140%	115%	129%	114
After 15 min	148%	136%	142%	117
After 30 min	137%	154%	143%	105
Control	125 ±9%		95 ±22	
After 2 min	124 ±10%	§[	115 ±27	]§
After 15 min	125 ±15%		103 ±16	
After 30 min	129 ±13%		92 ±21	

Abbreviations: SNRT, sinus node recovery time; SACT, sinoatrial conduction time.
Significance of difference from control: §P < 0·05.

Results

No untoward side effects were observed after intravenous administration of metoprolol. Its effects on sinus cycle length and conduction intervals are listed in Table 2, those on sinus node recovery time and sinoatrial conduction time in Table 3, and those on refractoriness and Wenckebach point are listed in Table 4.

SINUS NODE FUNCTION
(a) Sinus cycle length was prolonged in 14 cases (87%) increasing from an average value of 902 ±126 ms to 995 ±106 ms (P < 0·02), 985 ±115 ms (P < 0·05), and 961 ±116 ms (P < 0·05) after 2, 15, and 30 minutes, respectively. (b) Control sinus node recovery time (mean of calculated values for the three rates of atrial pacing) was 125 ±9 per cent. It was 124 ±10 per cent, 125 ±15 per cent, and 129 ±13 per cent 2, 15, and 30 minutes, respectively, after metoprolol (not significant).

SINOATRIAL CONDUCTION
Sinoatrial conduction time increased (Fig. 1) from the average value of 95 ±22 ms to 115 ±27 ms (P < 0·05), 103 ±16 ms (P < 0·05), and 92 ±21 ms (not significant) after 2, 15, and 30 minutes, respectively.

INTRA-ATRIAL CONDUCTION AND
ATRIUM REFRACTORY PERIODS
Intra-atrial conduction time (PA interval) was not modified by metoprolol. Mean values of atrium effective refractory period varied from 240 ±33 ms to 242 ±33 ms, 245 ±39 ms, and 241 ±35 ms, respectively, after 2, 15, and 30 minutes (not significant). Atrial functional refractory period varied from 289 ±31 ms to 298 ±33 ms, 296 ±29 ms, and 298 ±29 ms, respectively, after 2, 15, and 30 minutes (not significant).

INTRANODAL CONDUCTION AND
NODAL REFRACTORY PERIODS
AH interval was prolonged in 11 cases (68%). The increase was in the range of 5 to 20 ms; average values varied from 90 ±17 ms to 97 ±16 ms (P < 0·01), 98 ±17 ms (P < 0·01), and 97 ±18 ms (P < 0·01) after 2, 15, and 30 minutes, respectively. AV node effective refractory period (Fig. 2), measured in the control study in 3 cases, was increased by 10 to 60 ms. In another 2 cases, it was determined only after metoprolol and it was 40 to 80 ms longer than the atrial effective refractory period. Functional refractory period of the AV node increased in 9 cases (81%), the increase ranging between 10 and 90 ms. Mean values increased from 446 ±43 ms to

Table 4 *Effects of metoprolol on refractoriness and Wenckebach point in man**

Cases		S_1–S_1	Atrium ERP	Atrium FRP	AV node ERP	AV node FRP	His-Purkinje system ERP	His-Purkinje system FRP	RBB RRP	LBB RRP	Wenckebach point (beats/min)
1	Control	750	230	280	360	560			570		115
	After 2 min	750	230	300	410	620					107
	After 15 min	750	210	300	410	610					107
	After 30 min	750	210	300	400	600					107
2	Control	750	180	240	320	450					133
	After 2 min	750	200	270	370	520					130
	After 15 min	750	200	270	370	520					130
	After 30 min	750	200	280	380	540					130
3	Control	700	200	240		430					156
	After 2 min	700	200	240	320	440					150
	After 15 min	700	200	240	320	470					146
	After 30 min	700	200	240	320	460					140
4	Control	800	210	280		430				470	200
	After 2 min	800	210	280		450				470	192
	After 15 min	800	210	280		450				470	192
	After 30 min	800	210	280		430				470	192
5	Control	800	230	280		410	470	470			172
	After 2 min	800	220	280		410	470	490			162
	After 15 min	800	220	280		410	470	480			162
	After 30 min	800	220	280		410	470	480			162
6	Control	750	270	300	310	400	410				172
	After 2 min	750	280	310	320	410	420				158
	After 15 min	750	280	310	320	410	420				158
	After 30 min	750	280	310	320	410	420				154
7	Control	750	270	300		470					133
	After 2 min	750	270	320		500					120
	After 15 min	750	280	320		500					117
	After 30 min	750	270	330		520					120
8	Control	800	280	350		470					162
	After 2 min	800	290	370		500					143
	After 15 min	800	300	350		500					146
	After 30 min	800	290	350		490					146
9	Control	800	280	320		440	440			440	172
	After 2 min	800	280	320		440	440			440	167
	After 15 min	800	300	320		440	440			440	172
	After 30 min	800	280	320		440	440			440	172
10	Control	850	240	290		430				510	178
	After 2 min	850	240	290		470				510	162
	After 15 min	850	240	290		470				510	162
	After 30 min	850	240	290		470				510	162
11	Control	800	250	300		420					185
	After 2 min	800	250	300	340	470					163
	After 15 min	800	260	300	340	470					160
	After 30 min	800	250	300	340	470					160
	Control		240 ±33	289 ±31		†[446 ±43					161 ±25
	After 2 min		242 ±33	298 ±33		†[475 ±59] †					150 ±24†
	After 15 min		245 ±39	296 ±29		477 ±56					150 ±24†
	After 30 min		241 ±35	298 ±29		476 ±58					149 ±24†

*All values in ms.
Abbreviations: ERP, effective refractory period; FRP, functional refractory period; RRP, relative refractory period; RBB, right bundle-branch; LBB, left bundle-branch.
Significance of difference from control: †P < 0·01.

475 ±59 ms, 477 ±56 ms, and 476 ±58 ms after 2, 15, and 30 minutes, respectively (P < 0·01).

Wenckebach point was lowered in all cases (Fig. 3). Mean values varied from 161 ±25 beats/min to 150 ±24, 150 ±24, and 149 ±24 beats/min after 2, 15, and 30 minutes, respectively (P < 0·01).

INFRANODAL CONDUCTION

No modifications were observed with regard to HV interval, functional refractory period of the His-Purkinje system measured in 2 cases, relative refractory period of the right bundle-branch measured in 2 cases, relative refractory period of the left bundle-branch measured in 3 cases, and of QRS duration.

Discussion

Intravenous 0·1 mg/kg metoprolol in human subjects with estimated normal impulse formation and conduction produced significant changes in sinus cycle length and AV nodal conduction and refractoriness.

Mean sinus cycle length was prolonged by 10 per cent, a figure which has also been observed after intravenous 0·08 mg/kg pindolol (Di Biase *et al.*, 1977a) and 0·1 mg/kg oxprenolol (Di Biase *et al.*, 1977b), whereas intravenous 0·1 mg/kg propranolol was found to produce a 16 per cent increase (Stern and Eisenberg, 1969). However, as was noted with
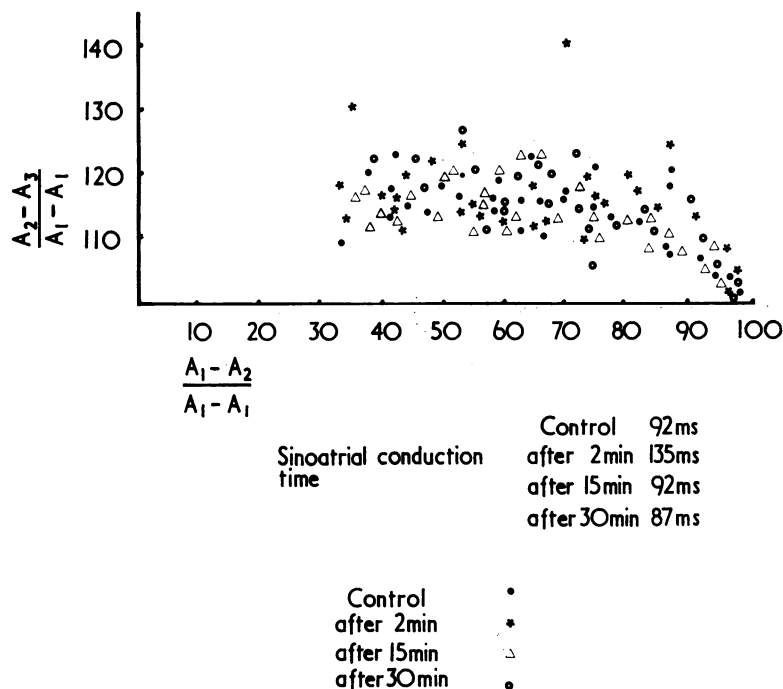
Fig. 1 *Effects of atrial premature stimulation on spontaneous sinus rhythm under control conditions and after metoprolol administration. The estimated sinoatrial conduction time is slightly increased.*
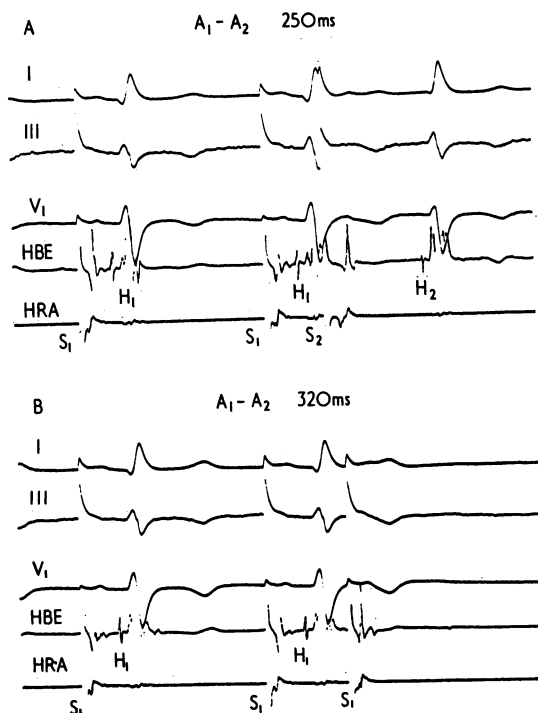
Sinoatrial conduction time

Control	92 ms
after 2 min	135 ms
after 15 min	92 ms
after 30 min	87 ms

Control	•
after 2 min	*
after 15 min	△
after 30 min	○

Fig. 2 *Effects of metoprolol on effective refractory period of the AV node. Leads I, III, and V_1, His bundle electrogram (HBE) and right atrial electrogram (HRA). In this subject at paced cycle length of 700 ms an atrial premature depolarisation A_2, delivered at a coupling interval of 250 ms, is still conducted to the His bundle (Panel A). Fifteen minutes after metoprolol, A_2 delivered at an A_1-A_2 coupling interval of 320 ms is blocked within the AV node (Panel B). The effective refractory period of the AV node is increased by 80 ms.*
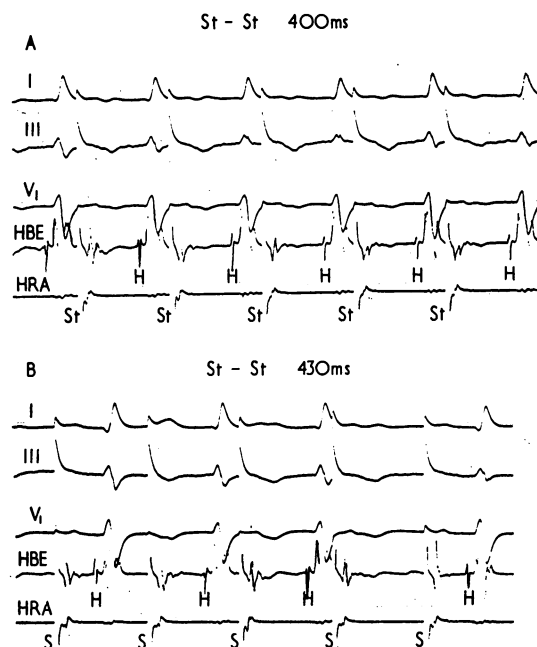
Fig. 3 *Effects of metoprolol on the Wenckebach point. In Panel A (control) I :I AV conduction is still present at an atrial paced cycle length of 400 ms (150 beats/ min). Fifteen minutes after metoprolol (Panel B), the Wenckebach point is reached at an atrial paced cycle length of 430 ms (140 beats/min).*

pindolol by Di Biase *et al.* (1977a) and with oxprenolol by Di Biase *et al.* (1977b), no depression of sinus node intrinsic automaticity seems to occur as suggested by the unchanged sinus node recovery time. Sinoatrial conduction time was slightly prolonged (P < 0·05 only in the determination at 2 and 15 min), a change also found with oxprenolol (Di Biase *et al.*, 1977b) and pindolol (Di Biase *et al.*, 1977a).

Intra-atrial conduction was not modified. Atrial refractoriness was not increased. This lack of effect was found to characterise oxprenolol (Di Biase *et al.*, 1977b), whereas propranolol produced a mild increase (Seides *et al.*, 1974) and pindolol a distinct increase (Di Biase *et al.*, 1977a) in atrial refractoriness.

Intranodal conduction is much depressed as proved by the significant (P < 0·01) increase of the AH interval and the lowering of the Wenckebach point. A consistent prolongation of effective and functional (P < 0·01) AV node refractory periods adds a further element in favour of the strong activity of this drug on the AV node. This effect seems common to most β-blocking agents since it is equally present in propranolol (Seides *et al.*, 1974), pindolol (Di Biase *et al.*, 1977a), and oxprenolol (Di Biase *et al.*, 1977b).

The infranodal conduction system is not affected, as shown by unchanged HV interval and unchanged His-Purkinje and bundle-branch refractory periods. In this respect again, metoprolol behaves similarly to the other β-blocking agents.

Because of these electrophysiological properties it may be concluded that metoprolol is a useful drug for controlling sinus tachycardia, ventricular rate in atrial flutter and fibrillation, and for the treatment and prophylaxis of AV nodal re-entrant supraventricular tachycardias. Some caution is to be recommended should it be used in heavy dosages and/or for long periods in subjects with clinical and/or electrocardiographic suspicion of sinus node dysfunction, whereas it should be avoided in subjects with chronic or paroxysmal AV node conduction defects.

On the other hand, the lack of adverse effects on the His-Purkinje system allows the use of this drug also in subjects with intraventricular conduction disturbances.

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